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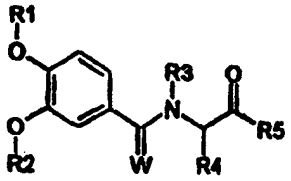
(54) Title: CATECHOL AMINO ACID DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

A phosphodiesterase IV inhibiting catechol derivative of general formula (I) or a pharmaceutically acceptable salt thereof in which R1, R2, R3, R4, R5 and W are as defined herein. In addition, a process for producing the compound of general formula (I) and a pharmaceutical composition containing pharmaceutically effective amount of the compound of general formula (I) are disclosed.



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CATECHOL AMINO ACID DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

FIELD OF THE INVENTION

The present invention relates to novel cathecol amino acid derivatives which inhibit the enzymatic activity of phosphodiesterase IV or tumor necrosis factor. These compounds may be useful in prevention or treatment of bronchial asthma, arthritis, bronchitis, chronic atretic airway, psoriasis, allergic rhinitis, dermatitis, AIDS, Crohn's disease, septicemia, septic shock, other inflammatory diseases such as cachexia, TNF related diseases, etc. Also, the present invention relates to a method for producing the said compounds and a pharmaceutical composition containing the said compounds.

BACKGROUND OF THE INVENTION

Phosphodiesterase IV is an enzyme that specifically hydrolyzes cAMP (adenosine 3',5'-cyclic monophosphate) into inactive adenosine 3',5'-monophosphate. The cAMP has been shown to be a second messenger mediating the cellular responses to external stimuli and to act as relaxing or contradicting bronchial muscles.

The inhibition of phosphodiesterase IV leads to the prevention of broncospasm by maintaining the concentration of cAMP and also induces an anti-inflammation. Therefore, compounds that inhibit phosphodiesterase IV should be effective in treating asthma and the like diseases.

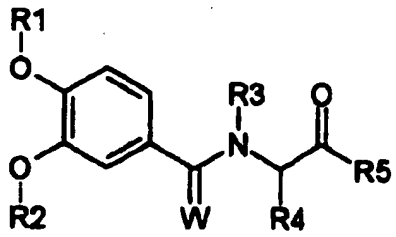
It is known that tumor necrosis factor (TNF) is implicated in infectious disease such as cachexia and autoimmune disease. Also TNF appears

to act as a primary mediator for inflammatory reaction such as septicemia and septic shock.

Therefore, it is expected that compounds with the inhibitory activity against phosphodiesterase IV or TNF will be pharmaceutically valuable and there is always a need to develop new compounds which inhibit phosphodiesterase IV and TNF.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a compound of the general formula I:



Formula I

or a pharmaceutically acceptable salt or solvate thereof in which

R1 represents methyl, ethyl, difluoromethyl or trifluoromethyl; **R2** represents C_1-C_7 alkyl optionally substituted with nitro or halogen, C_3-C_7 cycloalkane optionally substituted with nitro or halogen, phenyl optionally substituted with nitro or halogen, C_2-C_5 heteroaryl including N, O or S optionally substituted with nitro or halogen; **R3** represents hydrogen, hydroxy, C_1-C_6 alkyl or phenyl substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro or halogen; **R4** represents hydrogen, trifluoromethyl, C_1-C_6 alkyl, $-(CH_2)_nCO_2H$, $-(CH_2)_nCONH_2$, $-(CH)_n$ phenyl, $-(CH)_n$ phenylalcohol, $-(CH_2)_n$ indole, $-(CH_2)_n$imidazole, $-(CH_2)_xOH$,

$-(CH_2)_xSH$, $-(CH)_xS$ C_1-C_6 alkyl, $-(CH_2)_xNHC(NH)NH_2$ or $-(CH_2)_xNH$ in which x is 1 to 5 and n is 0 to 5; or **R3** and **R4** are together taken with C_1-C_4 to form a ring; **R5** represents NR6R7, -OR8 or -OCH(R8)OCOR9 in which R6 and R7 are each independently hydrogen, C_1-C_6 alkyl or phenyl substituted with C_1-C_4 alkoxy, nitro or halogen and R8 and R9 are each independently C_1-C_8 alkyl, C_3-C_{11} cycloalkyl substituted with halogen, nitro, hydroxy, C_1-C_4 alkyl or C_1-C_4 alkoxy or phenyl substituted with halogen, nitro, hydroxy, C_1-C_4 alkyl or C_1-C_4 alkoxy; and **W** represents oxygen or sulfur.

In another aspect, the present invention provides a process for producing the above compound of the general formula I.

In still another aspect, the present invention provides a pharmaceutical composition comprising pharmaceutically effective amount of the present compound of the general formula I or pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

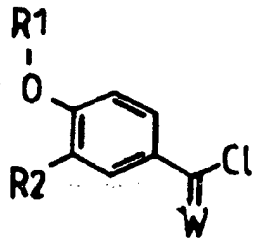
The preferred compounds of the present invention are those wherein R1 is methyl; R2 is cyclopentyl or norbonyl; R3 is hydrogen; R4 is hydrogen, C_1-C_4 alkyl or CH_3SH; or R3 and R4 are together taken with C_4 to form a ring; R5 is NR6R7, -OR8 or $-OCH(R8)OCO_2R9$ in which R6 and R7 are each independently hydrogen or C_1-C_4 alkyl and R8 and R9 are each independently C_1-C_4 alkyl; and W is oxygen.

The more preferred compounds of the present invention are as follows:

ethyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)-3-sulfamyl-(2S)-propanoate;

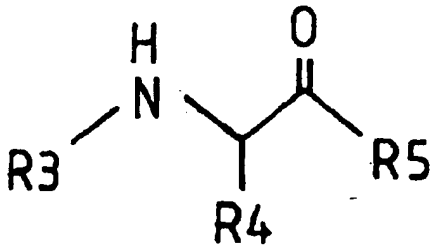
1N-carbamoylmethyl-3-cyclopentyloxy-4-methoxybenzylamide; and
ethyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)acetate.

The process for producing the compound of the general formula I according to the present invention comprises reacting a compound of the general formula II:



Formula II

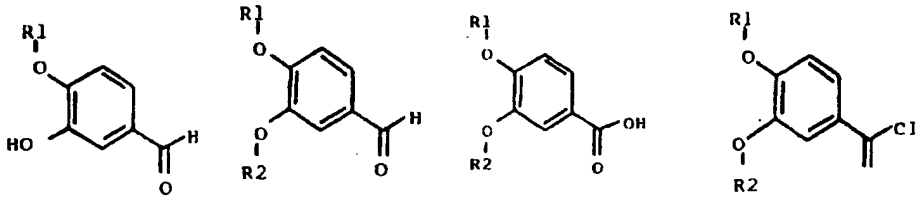
in which R1, R2 and W represent the same as defined above, with a compound of the general formula III:



Formula III

in which R3, R4 and R5 are the same as defined above, to produce the compound of the general formula I.

The above compound II was obtained by known method (J. Med. Chem. 1994, 37, 1696). This method is represented by the following reaction scheme:



The above compound III is commercially available.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. Therefore, the present invention provides in a further aspect pharmaceutical compositions comprising a novel compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of formula I may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula I and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier, for example an aqueous solvent such as water, ethanol or glycerine, or a

non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device.

Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The invention will now be described with reference to the following illustrative Examples.

EXAMPLES

REFERENCE EXAMPLE 1

3-Cyclopentyloxy-4-methoxybenzylaldehyde

50 g of isovanillin was added dropwise to 300 ml of

dimethylformamide and, then, 70 g of anhydrous potassium carbonate and 1.5 g of potassium iodide were added to form a supension. The suspension was stirred at 65℃ for 30 minutes. 63 g of cyclopentyl bromide was added dropwise to the suspension over 1 hour and was stirred at 65℃ for 1 day. After cooling to room temperature, the suspension was diluted by adding 1 L of toluene and, then, was washed with 1 N sodium hydroxide (2x500 ml) and distilled water (2x250 ml) in succession. The organic layer was dried over anhydrous sodium sulfate and was concentrated under reduced pressure to obtain 58 g of the title compound (yield: 80%).

^{1}H NMR($CDCl_3$, δ): 9.84(1H,s), 7.42(2H,m), 6.94(1H,D,J=9Hz), 4.87(1H,m), 3.93(3H,s), 2.1-1.6(8H,m)

REFERENCE EXAMPLE 2

3-Cyclopentyloxy-4-methoxybenzoic acid

35 g of sulfamic acid was added dropwise to a solution of 58 g of 3-cyclopentyloxy-4-methoxybenzylaldehyde in 450 ml of 80% acetic acid. Then, a solution of 30 g of 80% sodium chloride in 450 ml of distilled water was added dropwise to the suspension over 1 hour while maintaining the reaction temperature to 18℃-20℃. The reaction solution was stirred for 1 hour and was diluted by adding dropwise 450 ml of distilled water over 30 minutes. The solution was filtered with distilled water and was dried to obtain 56 g of white solid title compound (yield: 90%).

^{1}H NMR($CDCl_3$, δ): 7.73(1H,dd,J=9,1Hz), 7.24(2H,d,J=1Hz), 6.92(1H,d,J=9Hz), 4.84(1H,m), 3.93(3H,s), 2.1-1.6(8H,m)

REFERENCE EXAMPLE 3

3-Cyclopentyloxy-4-methoxybenzoic acid chloride

54 g of 3-cyclopentyloxy-4-methoxybenzoic acid was added to 30 ml

of thiochloride and was stirred for 5 hours. 50 ml of toluene was added to the reaction solution and was concentrated under reduced pressure to obtain 58 g of the dense brown title compound (yield: 98%).

^{1}H NMR($CDCl_3$, δ): 7.82(1H,dd,J=9,1Hz), 7.53(1H,d,J=1Hz), 6.92(1H,d,J=9Hz), 4.9-4.8(1H,m), 3.87(3H,s), 2.1-1.9(2H,m), 1.9-1.7(4H,m), 1.7-1.5(2H,m)

EXAMPLE 1

Ethyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)-3-phenyl-(2S)-propanoate

10 ml of pyridine was added dropwise to 400 mg of L-phenylalanine to form a suspension. 500 mg of 3-cyclopentyloxy-4-methoxybenzoic acid chloride (Reference Example 3) was added dropwise to the suspension and was refluxed for 4 hours. The reaction solution was concentrated under reduced pressure, diluted with dichloromethane and washed with 1N hydrochloric acid, saturated sodium bicarbonate and sodium chloride in succession. The organic layer was dried and concentrated under reduced pressure. The solid compound obtained therefrom was recrystallized with toluene to yield 630 mg of the solid thin yellow title compound. m.p. 105-107℃

1H NMR(DMSO-d_6, δ): 7.23(1H,d), 7.20(4H,m), 7.05(2H,m), 6.72(1H,H,d), 6.40(1H,d), 4.90(1H,ddd), 4.70(1H,m), 4.12(2H,q), 3.77(3H,s), 3.12(2H,ddd), 1.76(6H,m), 1.40(2H,m), 1.12(3H,t)

EXAMPLE 2

Ethyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)-3-sulfanyl-(2S)-propanoate

321 mg of L-cysteine ethylester was reacted with 400 mg of 3-cyclopentyloxy-4-methoxybenzoic acid chloride (Reference Example 3) in the

same manner as described in Example 1 to yield 600 mg of the title compound. m.p. 54-56℃

1H NMR($CDCl_3$, δ): 7.60(1H,dd), 7.41(1H,d), 7.41(1H,d), 7.38(1H,d), 6.80(1H,d), 5.00(1H,ddd), 4.85(1H,m), 4.25(2H,q), 3.84(3H,s), 3.65(1H,ddd), 3.17(1H,ddd), 1.70(8H,m), 1.28(3H,t)

EXAMPLE 3

1N-[1-carbamoyl-2-phenyl-(1S)-ethyl-3-cyclopentyloxy-4-methoxybenzylamide

10 ml of ammonium hydroxide was added to a solution of 780 mg of ethyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)-3-phenyl-(2S)-propanoate (Example 1) in 50 ml of methanol and was refluxed for 10 hours. After cooling the reaction solution, the solids formed was filtered and recrystallized with toluene to yield 450 mg of the solid white title compound. m.p. 139-140℃

1H NMR(DMSO-d_6, δ): 8.69(1H,d), 7.43(1H,d), 7.25(5H,m), 7.20(1H,dd), 6.99(1H,d), 4.80(1H,m), 4.62(1H,m), 3.79(3H,s), 3.13(2H,ddd), 1.75(8H,m)

EXAMPLE 4

1N-carbamoylmethyl-3-cyclopentyloxy-4-methoxybenzylamide

385 mg of glycineamide hydrochloride was reacted with 1.0 g of 3-cyclopentyloxy-4-methoxybenzoic acid chloride (Reference Example 3) in the same manner as described in Example 1 to yield 600 mg of the white title compound. m.p. 131-132℃

1H NMR($CDCl_3$, δ): 7.45(1H,d), 7.38(1H,dd), 7.2-7.0(1H,brs), 6.89(1H,d), 6.5-6.3(1H,brs), 5.7-5.5(1H,brs), 5.0-4.8(1H,m), 4.18(2H,d), 3.91(3H,s), 2.1-1.8(4H,m), 1.8-1.6(2H,m)

EXAMPLE 5

Ethyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)acetate

490 mg of glycine ethylester hydrochloride was reacted with 1.0 g of 3-cyclopentyloxy-4-methoxybenzoic acid chloride (Reference Example 3) in the same manner as described in Example 1 to yield 950 mg of the light yellow title compound. m.p. 73-74℃

1H NMR($CDCl_3$, δ): 7.50(1H,d), 7.41(1H,dd), 6.95(1H,d), 6.7-6.6(1H,brs), 5.9-5.8(1H,m), 4.34(2H,q), 4.30(2H,d), 3.97(3H,s), 2.0-1.6(8H,m), 1.40(3H,t)

EXAMPLE 6

Methyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)-4-methyl-(2S)-pentanoate

785 mg of L-leucine ethylester hydrochloride was reacted with 1.0 g of 3-cyclopentyloxy-4-methoxybenzoic acid chloride (Reference Example 3) in the same manner as described in Example 1 to yield 900 mg of the white title compound. m.p. 123-124℃

1H NMR($CDCl_3$, δ): 7.43(1H,d), 7.29(1H,dd), 6.87(1H,d), 6.43(1H,d), 4.9-4.7(1H,m), 3.90(3H,s), 3.78(3H,s), 2.0-1.6(11H,m), 1.01(3H,d), 0.99(3H,d)

EXAMPLE 7

1-(3-cyclopentyloxy-4-methoxybenzoyl)-(2S)-perhydro-2-pyrrolecarboxylamide

460 mg of L-prolineamide was reacted with 1.0 g of 3-cyclopentyloxy-4-methoxybenzoic acid chloride (Reference Example 3) in the same manner as described in Example 1 to yield 500 mg of the white title compound. m.p. 170-171℃

1H NMR($CDCl_3$, δ): 7.2-7.0(2H,m), 7.0-6.8(1H,brs), 6.89(1H,d), 5.7-5.5(1H, brs), 4.9-4.8(2H,m), 3.90(3H,s), 3.8-3.6(2H,m), 2.6-2.4(1H,m), 2.2-1.6(11H,m)

EXAMPLE 8

Methyl-1-(3-cyclopentyl-4-methoxybenzoyl)-(2S)-perhydro-2-pyrrolecarboxyl-ester

670 mg of L-prolinemethylester was reacted with 1.0 g of 3-cyclopentyloxy-4-methoxybenzoic acid chloride (Reference Example 3) in the same manner as described in Example 1 to yield 500 mg of the liquid colorless title compound.

^{1}H NMR($CDCl_3$, δ): 7.2-7.0(2H,m), 6.78(1H,d), 4.9-4.8(1H,m), 4.7-4.6(1H,m), 3.90(3H,s), 3.78(3H,s), 3.8-3.6(2H,m), 2.2-1.6(12H,m)

EXPERIMENTAL EXAMPLE

Inhibition of phosphodiesterase IV activity

Compounds prepared by Examples 1 to 7 and Rolipram as control were tested on the inhibition of phosphodiesterase IV.

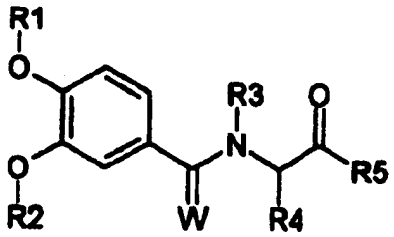
Phosphodiesterase IV partially purified from human U937 cells, test compound and 1.0 μM cAMP including 0.01 μM [^{3}H] cAMP were incubated at 30℃ for 20 minutes. The PDE reaction to convert cAMP into AMP was completed by boiling the reaction solution for 2 minutes. AMP was converted into adenosine by adding snake venom nucleotidase and incubating the reaction solution at 30℃ for 10 minutes. While unhydrolyzed cAMPs were bonded to AG1-X2 resin, the [^{3}H] adenosine in the aqueous solution was quantified by scintillation counting. The results are shown in Table II below, in which the values indicate inhibition(%) of the PDE IV by each test compound.

Table I

Test Compound	Example No.							Rolipram
	1	2	3	4	5	6	7	
Inhibition(%)	74.5	38.2	72.4	36.5	74.7	77.9	65.6	59.7

WHAT IS CLAIMED IS:

1. A compound of the general formula I:



Formula I

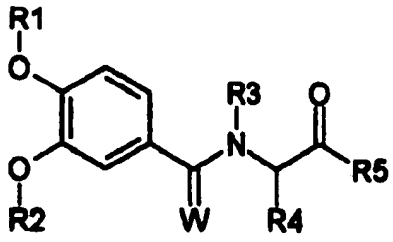
or a pharmaceutically acceptable salt or solvate thereof in which **R1** represents methyl, ethyl, difluoromethyl or trifluoromethyl; **R2** represents C_1-C_7 alkyl optionally substituted with nitro or halogen, C_3-C_7 cycloalkane optionally substituted with nitro or halogen, phenyl optionally substituted with nitro or halogen, C_2-C_5 heteroaryl including N, O or S optionally substituted with nitro or halogen; **R3** represents hydrogen, hydroxy, C_1-C_6 alkyl or phenyl substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro or halogen; **R4** represents hydrogen, trifluoromethyl, C_1-C_6 alkyl, $-(CH_2)_nCO_2H$, $-(CH_2)_nCONH_2$, $-(CH)_n$ phenyl, $-(CH)_n$ phenylalcohol, $-(CH_2)_n$ indole, $-(CH_2)_n$imidazole, $-(CH_2)_xOH$, $-(CH_2)_xSH$, $-(CH)_xS$ C_1-C_6 alkyl, $-(CH_2)_xNHC(NH)NH_2$ or $-(CH_2)_xNH$ in which x is 1 to 5 and n is 0 to 5; or **R3** and **R4** are together taken with C_1-C_4 to form a ring; **R5** represents NR6R7, -OR8 or -OCH(R8)OCOR9 in which R6 and R7 are each independently hydrogen, C_1-C_6 alkyl or phenyl substituted with C_1-C_4 alkoxy, nitro or halogen and R8 and R9 are each independently C_1-C_8 alkyl, C_3-C_{11} cycloalkyl substituted with halogen, nitro, hydroxy, C_1-C_4 alkyl or C_1-C_4 alkoxy or phenyl substituted with halogen, nitro, hydroxy, C_1-C_4 alkyl or C_1-C_4 alkoxy; and **W** represents oxygen or sulfur.

2. The compound of claim 1 wherein R1 is methyl; R2 is cyclopentyl or norbonyl; R3 is hydrogen; R4 is hydrogen, C_1-C_4 alkyl or CH_3SH; or R3 and R4 are together taken with C_4 to form a ring; R5 is NR6R7, -OR8 or -OCH(R8)OCO_2R9 in which R6 and R7 are each independently hydrogen or C_1-C_4 alkyl and R8 and R9 are each independently C_1-C_4 alkyl; and W is oxygen.

3. The compound of claim 1 which is in the form of optical isomer or geometrical isomer.

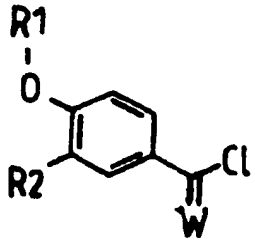
4. The compound of claim 1 which is ethyl-2-(3-cyclopentyloxy-4-methoxyphenylcarboxylamido)-3-phenyl-(2S)-propanoate, ethyl-2-(3-cyclopentyl-oxy-4-methoxyphenylcarboxylamido)-3-sulfanyl-(2S)-propanoate, 1N-[1-carbamoyl-2-phenyl-(1S)-ethyl-3-cyclopentyloxy-4-methoxybenzylamide, 1N-carbamoylmethyl -3-cyclopentyloxy-4-methoxybenzylamide, ethyl-2-(3-cyclopentyloxy-4-methoxy-phenylcarboxylamido)acetate, methyl-2-(3-cyclopentyloxy-4-methoxyphenyl-carboxylamido)-4-methyl-(2S)-pentanoate, 1-(3-cyclopentyloxy-4-methoxybenzoyl)-(2S)-perhydro-2-pyrrolecarboxylamide, or methyl-1-(3-cyclopentyl-4-methoxy-benzoyl)-(2S)-perhydro-2-pyrrolecarboxylester.

5. A process for producing a compound of the general formula I:



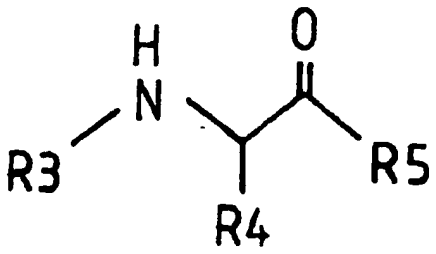
Formula I

or a pharmaceutically acceptable salt or solvate thereof in which **R1** represents methyl, ethyl, difluoromethyl or trifluoromethyl; **R2** represents C_1-C_7 alkyl optionally substituted with nitro or halogen, C_3-C_7 cycloalkane optionally substituted with nitro or halogen, phenyl optionally substituted with nitro or halogen, C_2-C_5 heteroaryl including N, O or S optionally substituted with nitro or halogen; **R3** represents hydrogen, hydroxy, C_1-C_6 alkyl or phenyl substituted with C_1-C_4 alkyl, C_1-C_4 alkoxy, nitro or halogen; **R4** represents hydrogen, trifluoromethyl, C_1-C_6 alkyl, $-(CH_2)_nCO_2H$, $-(CH_2)_nCONH_2$, $-(CH)_n$ phenyl, $-(CH)_n$ phenylalcohol, $-(CH_2)_n$ indole, $-(CH_2)_n$imidazole, $-(CH_2)_xOH$, $-(CH_2)_xSH$, $-(CH)_xS$ C_1-C_6 alkyl, $-(CH_2)_xNHC(NH)NH_2$ or $-(CH_2)_xNH$ in which x is 1 to 5 and n is 0 to 5; or **R3** and **R4** are together taken with C_1-C_4 to form a ring; **R5** represents NR6R7, -OR8 or -OCH(R8)OCOR9 in which R6 and R7 are each independently hydrogen, C_1-C_6 alkyl or phenyl substituted with C_1-C_4 alkoxy, nitro or halogen and R8 and R9 are each independently C_1-C_8 alkyl, C_3-C_{11} cycloalkyl substituted with halogen, nitro, hydroxy, C_1-C_4 alkyl or C_1-C_4 alkoxy or phenyl substituted with halogen, nitro, hydroxy, C_1-C_4 alkyl or C_1-C_4 alkoxy; and **W** represents oxygen or sulfur, which comprises reacting a compound of the general formula II:



Formula II

in which R1, R2 and W represent the same as defined above, with a compound of the general formula III:



Formula III

in which R3, R4 and R5 represent the same as defined above, to produce the said compound of the general formula I.

6. A pharmaceutical composition useful in the inhibition of phosphodiesterase IV or tumor necrosis factor comprising pharmaceutically effective amount of the compound according to claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00156

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 C 235/52,237/22; C 07 D 207/16; C 07 C 323/02,231/02; A 61 K 31/22, 31/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 C 253/52,237/22,323/59,231/02; C 07 D 207/16; A 61 K 31/22,31/165

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Vol.105, No.11, 15 September 1986 (Columbus, Ohio, USA), page 88, column 1, abstract No.91509y, MAKOVEC, F. et al.:"New glutamic and aspartic derivatives with potent CCK-antagonistic activity", & Eur. J. Med. Chem.--Chim. Ther. 1986, 21(1), 9-20 (Eng). Chemical Abstracts, Eleventh Collective Index, Vol.96-105, FORMULAS, page 14736F, C20H30N2O6, Pentanoic acid, 4-[(3,4-dimethoxybenzoyl)amino]-5-(dipropylamino)-5-= oxo (±).	1
X	Chemical Abstracts, Vol.114, No.11, 18 March 1991 (Columbus, Ohio, USA), page 14, column 2, abstract No.94611x, COATS, E.A. et al.:"Correlation analysis and molecular modeling of cholecystokinin inhibitors", & Quant. Struct.-Act. Relat. 1990, 9(2), 94-101 (Eng). Chemical Abstracts, Twelfth Collective Index, Vol.106-115, FORMULAS, page 20045F, C20H30N2O6, Pentanoic acid, 4-[(3,4-dimethoxybenzoyl)amino]-5-(dipropylamino)-5-= oxo-(S).	1,3

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 1998 (23.01.98)	05 February 1998 (05.02.98)

Name and mailing address of the ISA/ AT	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00156

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, Vol.123, No.17, 23 October 1995 (Columbus, Ohio, USA), page 853, column 2, abstract No.313505g, PACE, R.D. et al.:"Allylboration of α-Amino Ketones", & J. Org. Chem. 1995, 60(15), 4838-44 (Eng).	1,3
	Chemical Abstracts, Vol.123, Formula Index, page 3109F, C19H21NO5, L-Phenylalanine, N-(3,4-dimethoxy= benzoyl)-methyl ester.	
X	Chemical Abstracts, Vol.123, No.17, 23 October 1995 (Columbus, Ohio, USA), page 1190, column 1, abstract No.228176f, OKURA, A. et al."Preparation of hetero= cyclic compounds as tyrosine kinase inhibitors", & WO 95/06 032 (BANYU PHARMACEUTICAL CO., LTD.).	1
	Chemical Abstracts, Vol.123, Formula Index, page 1943F, C13H17NO5, Glycine, N-(3,4-dimethoxybenzoyl)-= ethyl ester.	
X	Chemical Abstracts, Vol.99, No.23, 05 December 1983 (Columbus, Ohio, USA), page 738, column 2, abstract No.194796b, KNEFELI, F. et al.:"Electron-impact induced loss of C-5 and C-8 substituents in 1,2,3,4-= tetrahydroisoquinolines. I. Synthesis of 4-acetyl= pyrrolo 1,2-b isoquinoline", & Arch. Pharm. (Weinheim, Ger.) 1983, 316(9), 773-81 (Ger).	1,3
	Chemical Abstracts, Eleventh Collective Index, Volumes 96-105, Formulas, page 10025F, C15H19NO5, L-Prolin, 1-(3,4-dimethoxybenzoyl)-methyl ester.	
X	US 2 956 081 A (G.W. KUSSEROW) 11 October 1960 (11.10.60), column 1, line 55 - column 2, line 4; example 6.	1,5
X Y	EP 0 388 967 A1 (WAKAMOTO PHARMACEUTICAL CO.) 26 September 1990 (26.09.90), page 14, line 44.	1 5
Y A	WO 97/05 105 A1 (PFIZER INC.) 13 February 1997 (13.02.97), page 1, lines 8-36; page 7, lines 14-24.	5 1-3,6
A	WO 93/15 044 A1 (SMITH-KLINE BEECHAM CORPORATION) 05 August 1993 (05.08.93), pages 1,2.	6

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 97/00156

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 2956081		keine - none - rien	
EP A1 388967	26-09-90	DE C0 69020394	03-08-95
		DE T2 69020394	29-02-96
		EP B1 388967	28-06-95
		HU A0 901814	28-07-90
		HU A2 57744	30-12-91
		HU A3 9500234	28-09-95
		HU B3 211520	28-11-95
		US A 5055481	08-10-91
		US E 35281	18-06-96
		JP A2 4270271	25-09-92
WO 9705105		keine - none - rien	
WO A1 9315044	05-08-93	AU A1 35886/93	01-09-93